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Cigarette smoking and the risk of thyroid cancer

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Abstract

Thyroid cancer, whose aetiology is largely uncertain, has been negatively associated with cigarette smoking in a number of studies, possibly consistent with the greater occurrence of the disease in women than in men. This association was explored in the context of a Canadian case–control study of thyroid cancer. Newly diagnosed cases were identified primarily through provincial cancer registries in Canada and controls were identified from the general population. Data were collected through mailed questionnaires, yielding 1224 cases and 2659 controls. Reduced risk was observed for ever/never cigarette smoking (risk ratio estimate (RR) of 0.71 (95% confidence interval (CI) = 0.60–0.83) for females and 0.77 (95% CI = 0.58–1.02)) for males. Dose–response effects were observed with duration, quantity smoked and pack-years of exposure, although there was no decreasing protective effect with the age started smoking or years since stopped smoking. There is evidence of reduced risk for all histological subgroups. The protective effect of smoking may be due to a number of different mechanisms, including an effect on thyroid stimulating hormone and on oestrogen metabolism.

Keywords: Thyroid cancer; Cigarette smoking; Case–control study

1. Introduction

Over the course of the last 15 years, a number of studies have reported a reduced risk of thyroid cancer in women associated with cigarette smoking [1–8]. However, there has been little exploration of the particulars of the effect of smoking, since most of the studies did not report a significantly decreased risk. Furthermore, given that thyroid cancer occurs more frequently in women than in men (one of the few cancers which has a female preponderance), few of these studies have examined the effect of smoking in men. The analysis reported here used data from a national case–control study of thyroid cancer, conducted in Canada between 1986 and 1990 [9]. The main emphasis of the study was an examination of radiation exposure and thyroid cancer risk, but substantial data on other potential risk factors were also collected. Our aim was to reaffirm the effect of cigarette smoking on thyroid cancer risk in women, to examine that effect in men, and to undertake a histological-specific analysis to better understand the relationship between cigarette smoking and thyroid cancer.

2. Patients and methods

2.1. Data collection

Cases of carcinoma of the thyroid, newly diagnosed between January 1986 and December 1988, were eligible for inclusion in the study. Cases were identified through provincial cancer registries in eight provinces in Canada (Newfoundland, Nova Scotia, New Brunswick, Ontario, Manitoba, Saskatchewan, Alberta and British Columbia), and through hospital discharge records in one province (Quebec). Where possible, histological review of the case tissue was conducted by an independent pathologist.

Controls were stratified on the province of residence, sex and age, to match the expected province–sex–age distribution of the cases. Controls were selected from the general population of each province using different sources: from municipal assessment roles in Ontario, the

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telephone directory in Manitoba, the electoral roles in Quebec and Medicare files in the remaining six provinces.

Cases and controls received a mailed, self-administered questionnaire along with a stamped, addressed return envelope. Telephone follow-up was conducted 1 week after the initial mailing, and additional mailings were sent as requested by the subject. Following receipt of the questionnaire, telephone calls were made to clarify answers which were incomplete or inconsistent. Subject questionnaires included detailed assessment of radiation exposure (both diagnostic and therapeutic, as well as work-related); occupational, medical and residential histories; reproductive history for women; and cigarette smoking history.

Questionnaires were available for 3939 subjects, 1280 cases and 2659 controls (response rates of 80.0% and 60.1%, respectively), 810 of the cases (63%) were reviewed by an independent pathologist. Where the result of the review conflicted with that of the original hospital report, the tissue was reviewed by a second pathologist. The original hospital report was used as histological confirmation where there was no independent slide review, or where the second pathologist confirmed the original diagnosis. Otherwise, the classification by the first review was used. After review of the questionnaire and tissue data, 56 cases were excluded from analysis (42 due to a negative diagnosis of thyroid cancer following a review of the tissue), leaving 1224 cases. Information on smoking status was available for all subjects. For those who had ever smoked, the age at which they started smoking was missing for 0.6%, the number of cigarettes smoked for 0.9%, and the age at which they stopped smoking for 0.3%.

2.2. Data analysis

All analyses used conditional logistic regression [10] adjusting for age in 5-year age groups (and sex, where applicable). Using never-smokers as the reference category, sex-specific risk ratios and 95% confidence intervals (CI) were estimated for ever-smokers, age started smoking (<15, 15–19, 20–24 and >24 years of age), duration of smoking ($\leqslant 10$, 11–20, 21–30, and >30 years), quantity smoked ($\leqslant 10$, 11–19, 20–25 and >25 cigarettes per day), pack-years of exposure ($\leqslant 4$, 4.1–10, 10.1–25, and >25 pack-years), and years since stopped smoking (<3, 3–8, 9–15 and >15 years).

Smoking effects were estimated for sex or different histology groups by calculating separate risk ratios and 95% CI. Confounding by known risk factors was assessed by including any history of thyroid disease and radiation exposure in the multivariate logistic regression model and assessing the degree to which these altered the risk estimate associated with smoking. Variables included in the model were history of goitre, Hashimoto's disease (thyroiditis), overactive thyroid (hyperthyroidism, Graves' disease, thyroxicosis), underactive thyroid (hypothyroidism, myxoedema) and radiation exposure (ever exposed to radiotherapy, radioactive drugs or occupational radiation exposure). Reproductive factors including number of children, number of pregnancies and use of oral contraceptives were not associated with thyroid cancer risk (odds ratio (OR) estimates ranging from 0.99 to 1.1), and did not alter the estimates for smoking. They were, therefore, not included in the multivariate analysis.

3. Results

OR estimates and 95% CIs for ever-smoked and for various characteristics of smoking exposure are shown for females and males in Table 1. Ever having smoked cigarettes was associated with a reduced risk of thyroid cancer for both females (OR = 0.71, 95% CI = 0.60, 0.83) and males (OR = 0.77, 95% CI = 0.58, 1.02). Furthermore, reduced risks were seen for nearly every category of smoking exposure, as well as decreases in risk with increasing dose (number of cigarettes), duration (number of years smoked), and pack-years. There did not appear to be a trend of increasing risk associated with increasing years since stopping smoking or the age started smoking. When number of cigarettes and duration of smoking were both included in the model, there was no improvement of fit compared with the reduced model which used pack-years as the summary smoking measure.

Table 2 displays the ORs and 95% CIs by histological type. There is evidence of a reduced risk associated with ever having smoked for each of the histological types of thyroid cancer, although many of the 95% CIs include 1.0, and the numbers for some of the subtypes (especially medullary and anaplastic) are quite small.

A significant negative association with smoking was also found in the 42 cases excluded from analysis based on a negative diagnosis of thyroid cancer in the tissue review (data not shown). In an informal review of the Ontario cases determined not to be thyroid cancer, the reviewer often reported microcarcinoma. This suggests that smoking may have the same effect on the formation of occult tumours as it does on clinically significant tumours.

In a multivariate model which included the known risk factors for thyroid cancer, the reduced risk associated with ever having smoked was still in evidence (Table 3). In fact, there was little suggestion of confounding by a positive history of thyroid disease or radiation exposure, even though these factors were associated with large and statistically significant increases in the risk for thyroid cancer.

Table 1
Number of cases ($n=1224$) and controls ($n=2659$)[a] odds ratios (OR)[b] and 95% confidence intervals (CI) for thyroid cancer associated with characteristics of cigarette smoking

	Females				Males			
	Cases *n* (%) ($n=893$)	Controls *n* (%) ($n=1953$)	OR (95% CI)	Test for trend[c] (*P* value)	Cases *n* (%) ($n=331$)	Controls *n* (%) ($n=706$)	OR (95% CI)	Test for trend[c] (*P* value)
Never-smoked	529 (59.2)	1001 (51.3)	1.00		123 (37.2)	217 (30.7)	1.00	
Ever-smoked	364 (40.8)	952 (48.7)	0.71 (0.60, 0.83)		208 (62.8)	489 (69.3)	0.77 (0.58, 1.02)	
Missing data	0	0			0	0		
Age started smoking (years)[d]	($n=364$)	($n=952$)			($n=208$)	($n=489$)		
Missing data	3 (0.8)	5 (0.5)			1 (0.5)	4 (0.8)		
<15	44 (12.1)	111 (11.7)	0.75 (0.51, 1.08)		40 (19.2)	89 (18.2)	0.76 (0.48, 1.18)	
15–19	207 (56.9)	547 (57.5)	0.69 (0.57, 0.84)		112 (53.8)	286 (58.5)	0.70 (0.51, 0.97)	
20–24	66 (18.1)	186 (19.5)	0.63 (0.46, 0.85)		38 (18.3)	82 (16.8)	0.90 (0.56, 1.45)	
>24	44 (12.1)	103 (10.8)	0.83 (0.56, 1.21)		17 (8.2)	28 (5.7)	0.97 (0.49, 1.93)	
				n.s				n.s.
Number of years smoked[d]								
Missing data	4 (1.1)	9 (0.9)			2 (1.0)	4 (0.8)		
$\leqslant 10$	140 (38.5)	264 (27.7)	1.05 (0.82, 1.34)		41 (19.7)	66 (13.5)	1.09 (0.69, 1.71)	
11–20	96 (26.4)	259 (27.2)	0.68 (0.52, 0.89)		59 (28.4)	107 (21.9)	0.97 (0.65, 1.43)	
21–30	60 (16.5)	209 (22.0)	0.48 (0.35, 0.66)		45 (21.6)	121 (24.7)	0.68 (0.44, 1.05)	
>30	64 (17.6)	211 (22.2)	0.55 (0.40, 0.76)		61 (29.3)	191 (39.1)	0.49 (0.31, 0.78)	
				0.0003				0.0023
Number of cigarettes per day[d]								
Missing data	2 (0.5)	9 (0.9)			1 (0.5)	6 (1.2)		
$\leqslant 10$	139 (38.2)	291 (30.6)	0.91 (0.72, 1.14)		44 (21.2)	72 (14.7)	1.06 (0.67, 1.66)	
11–19	88 (18.0)	186 (19.5)	0.86 (0.65, 1.14)		36 (17.3)	70 (14.3)	0.95 (0.60, 1.52)	
20–25	105 (21.5)	351 (36.9)	0.54 (0.42, 0.69)		79 (38.0)	242 (49.5)	0.59 (0.42, 0.84)	
>25	30 (6.1)	115 (12.8)	0.46 (0.30, 0.70)		48 (23.1)	99 (20.2)	0.82 (0.53, 1.26)	
				0.0002				n.s.
Pack-years[d]								
Missing data	5 (1.4)	14 (1.5)			3 (1.4)	9 (1.8)		
$\leqslant 4.0$	117 (32.1)	225 (23.6)	1.02 (0.79, 1.31)		26 (12.5)	47 (9.6)	0.97 (0.57, 1.65)	
4.1–10	88 (24.2)	205 (21.5)	0.79 (0.60, 1.05)		41 (19.7)	65 (13.3)	1.14 (0.73, 1.80)	
10.1–25	100 (27.5)	305 (32.0)	0.58 (0.45, 0.75)		75 (36.1)	167 (34.2)	0.76 (0.53, 1.09)	
>25	54 (14.8)	203 (21.3)	0.46 (0.33, 0.64)		63 (30.3)	201 (41.1)	0.55 (0.36, 0.83)	
				0.0001				0.01
Years since stopped smoking								
Missing data	0	0			0	0		
Current/recent smoking (<3)	211 (58.0)	587 (61.7)	0.67 (0.55, 0.81)		96 (46.2)	244 (49.9)	0.71 (0.51, 0.98)	
Stopped 3–8 years ago	63 (17.3)	118 (12.4)	0.97 (0.70, 1.35)		30 (14.4)	64 (13.1)	0.88 (0.53, 1.45)	
Stopped 9–15 years ago	43 (11.8)	132 (13.9)	0.59 (0.41, 0.85)		30 (14.4)	85 (17.4)	0.60 (0.37, 0.98)	
Stopped >15 years ago	47 (12.9)	115 (12.1)	0.73 (0.51, 1.06)		52 (25.0)	96 (19.6)	0.92 (0.57, 1.48)	
				n.s.				n.s.

n.s., non-significant.
[a] Numbers may vary due to missing data.
[b] Adjusted for age (5-year age groups).
[c] Test for trend is among smokers.
[d] Never smoked is the referent category.

4. Discussion

Although relatively little is known about the aetiology of thyroid cancer beyond its association with radiation exposure and some previous thyroid disorders [11], data are slowly accumulating as to the protective effect of cigarette smoking on this disease. Our data indicate a generally consistent, albeit not always statistically significant, reduction in risk among both men and women, for various subtypes of thyroid cancer, regardless of the way that cigarette smoking was quantified. The association appeared not to be confounded by other risk

Table 2
Odds ratio[a] (OR) and 95% confidence interval (CI) for thyroid cancer risk associated with cigarette smoking, by sex and histology

	Females			Males			All
	Never-smoked *n* (%)	Ever-smoked *n* (%)	OR (95% CI)	Never-smoked *n* (%)	Ever-smoked *n* (%)	OR (95% CI)	OR[b] (95% CI)
Controls	1001	952		217	489		
All cases combined	529 (100)	364 (100)	0.71 (0.60, 0.83)	123 (100)	208 (100)	0.77 (0.58, 1.02)	0.72 (0.63, 0.83)
Histological type							
Papillary	423 (80.0)	305 (83.8)	0.73 (0.61, 0.87)	94 (76.4)	159 (76.4)	0.81 (0.60, 1.12)	0.75 (0.64, 0.87)
Follicular	73 (13.8)	41 (11.3)	0.61 (0.41, 0.91)	18 (14.6)	30 (14.4)	0.64 (0.34, 1.21)	0.62 (0.44, 0.87)
Medullary	13 (2.5)	10 (2.7)	0.76 (0.33, 1.75)	7 (5.7)	15 (7.2)	0.76 (0.30, 1.91)	0.76 (0.41, 1.41)
Anaplastic	9 (1.7)	2 (0.2)	0.30 (0.06, 1.41)	1 (0.8)	1 (0.5)	0.20 (0.01, 3.46)	0.27 (0.07, 1.10)
Other thyroid cancer	11 (2.1)	6 (0.6)	0.68 (0.24, 1.91)	3 (2.4)	3 (1.4)	0.37 (0.07, 1.89)	0.57 (0.23, 1.39)
Not thyroid cancer ($n=42$)	23 (55)	11 (26)	0.47 (0.23, 0.98)	3 (7)	5 (12)	0.70 (0.16, 3.20)	0.51 (0.27, 0.97)

[a] Adjusted for age (5-year age groups).
[b] Adjusted for sex and age.

factors for thyroid cancer. There appears to be a dose–response effect associated with both the number of cigarettes smoked per day and number of years smoked, although the risk estimates do not change monotonically. Finally, we did not see a particular attenuation of risk with those who had given up smoking (years since smoked), nor an increased effect among those who started smoking at very young ages.

Our findings are, in the main, consistent with the literature, where studies generally have reported reduced risk estimates associated with cigarette smoking among women, although most of these were not statistically significant [1,3,4,6,8,12]. The few studies which also included men [3,12] reported no reduced risk in that group. It is not clear why the results of Sokic and colleagues [13] indicated increased risk estimates, although this was the only hospital-based (i.e. hospital controls, rather than population controls) among these studies, so a biased control sample with respect to smoking exposure is possible. Galanti and colleagues [1] also reported a lower risk among young smokers, but no dose–response associated with the number of cigarettes or the number of years smoked.

Table 3
Estimated odds ratios (OR)[a] and 95% confidence intervals (CI) from multivariate logistic regression, by sex

	Females OR (95% CI)[a]	Males OR (95% CI)[a]
Ever smoked	0.71 (0.60, 0.84)	0.80 (0.60, 1.08)
History of goitre	4.79 (3.21, 7.13)	6.08 (2.34, 15.8)
History of Hashimoto's disease	12.43 (6.04, 25.6)	n.e.
History of overactive thyroid	1.79 (1.10, 2.91)	6.25 (2.24, 17.4)
History of underactive thyroid	1.20 (0.88, 1.64)	4.32 (1.56, 12.0)
Radiation exposure	1.64 (1.28, 2.10)	1.54 (0.97, 2.44)

n.e., not estimable as no controls reported with Hashimoto's disease.
[a] Adjusted for 5-year age groups and the other variables in the table.

A mechanism by which cigarette smoking might be protective for thyroid cancer is by lowering the endogenous levels of thyroid stimulating hormone (TSH) [14–17], although not all studies have reported this effect [18]. It has been suggested that increased levels of TSH are associated with an increased risk of thyroid cancer [11]. Thus, an agent which lowers TSH would then potentially protect against the disease. An additional explanation for the effect of smoking on thyroid cancer among women is suggested by studies which indicate that smoking may have an anti-oestrogenic effect [19]. However, there appears to be no evidence that smoking may act in a similar manner on androgen metabolism [20,21]. Thyroid cancer's preponderance among women has led to the hypothesis that oestrogen metabolism may play a role in its occurrence.

One of the limitations of the present study is the relatively low response rate among the population controls. While it is true that greater non-response provides greater opportunity for non-response bias, there is no evidence of this having occurred. The per cent of smokers in our data are very similar to that from the Canada-wide General Social Surveys: 35% of males and 30% of females in our sample, compared with 37% and 32%, respectively, in 1985, and 32% and 30%, respectively, in 1991 [22]. In addition, the known (and strong) risk factors for thyroid cancer appear to affect risk in the anticipated directions. In our data, both radiation exposure and prior thyroid disease were associated with an increased risk of thyroid cancer. Thus, although it is still possible that our control sample was biased in relation to cigarette exposure, this explanation is less tenable. Furthermore, studies suggest that smokers are over-represented among non-respondents (see, e.g. [23]). The direction of bias then, would be towards the null, indicating that we have underestimated the reduced risk of thyroid cancer associated with smoking.

We conclude, then, that the relationship between cigarette smoking and thyroid cancer is not spurious, and further exploration of a number of hypotheses might aid in the ultimate prevention of thyroid cancer. For instance, the age distribution of thyroid cancer differs from that of most adult cancers, and suggests that there may be a period in adolescence or early adulthood where the role of hormones in tumorigenesis is especially critical. Given the role of smoking as a modifier of hormone levels, more detailed smoking histories might enable this hypothesis to be investigated.

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